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Filed : March 19, 1999

Figures 1A-B; in the passage bridging pages 8 and 9; Example 1; and page 27, line 1 to page 29, line 14.

Claim rejections - 35 U.S.C § 101

Claims 72-73, 77, 81 and 85 previously pending in this application were rejected under 35 U.S.C. § 101 as allegedly being “not supported by either a specific and/or substantial asserted utility or a well established utility.” According to the Examiner, the disclosure on page 29 of the specification “merely invites others to experiment to discover what specific disease states may be treated from a laundry list” of utilities. The Examiner specifically refers to the statement in the full passage on lines 2-8 to the effect that “GFR α 3 or its agonist or antagonists can be used to treat conditions . . . “in support of the notion that one skilled in the art would not reasonably know which specific “conditions” could be treated, nor reasonably know what “agonists or antagonists” putatively exist, if later discovered. The ultimate basis for this rejection appears to be the belief that GFR α 3 was an orphan receptor at the time the present invention was made and, in the Examiner’s view, for this very reason it did not have any “real world” utility as of the filing date.

Claims 72, 73, 77, 81, and 85 stand cancelled, therefore the rejection of these claims under 35 U.S.C § 101 is moot.

New claims 86-97 are also believed to be directed to subject matter having patentable utility, as discussed in the following remarks.

The claimed invention

The claims pending in this application concern nucleic acid molecules encoding polypeptides having a well-defined degree of sequence identity with the native sequence murine GFR α 3 polypeptide of SEQ ID NO: 5, vectors comprising such nucleic acid molecules and host cells comprising such vectors. The claims additionally recite that the

encoded polypeptides have the ability to regulate peripheral neuronal function. A common feature of all claims is the use of a nucleic acid encoding a GFR α 3 polypeptide, and the question is whether Applicants have established at least one patentable utility for such nucleic acid. In particular, the question is whether Applicants have established that the claimed polypeptides have the ability to regulate peripheral neuronal function, and whether this qualifies as patentable utility.

Utility information provided in the present application

The present application includes disclosure concerning the function of GFR α 3, although the native ligand of GFR α 3 was unknown at the time of filing the present application. According to the expression data disclosed in Example 5, in the mouse GFR α 3 mRNA was very strongly expressed in dorsal root ganglia, in sympathetic ganglia, and in peripheral nerves. The vestibular ganglion also displayed strong signal. At later developmental stages, expression within the CNS was very limited. Human GFR α 3 showed a similar expression pattern, which, unlike the related GFR α 1 and GFR α 2 receptors, was very limited and localized (see Figure 8). According to page 47, lines 26-27, "*In situ* hybridization studies using DNA encoding mouse GFR α 3 revealed a pattern of expression in peripheral sensory neurons and sympathetic neurons." Based on these data, at page 29, lines 2-8, the specification teaches that "GFR α 3 . . . can be used to treat conditions involving dysfunction of the autonomic nervous system including, but not limited to, disturbances in blood pressure or cardiac rhythm, gastrointestinal function, impotence, and urinary continence."

Furthermore, on page 28, lines 15-33, applicants disclose that "Non-human homologues of GFR α 3 can be used to construct a GFR α 3 "knock out" animal which has a defective or altered gene encoding GFR α 3 as a result of homologous recombination between the endogenous gene encoding GFR α 3 and altered genomic DNA encoding GFR α 3 introduced into an embryonic cell of the animals. . . . Knockout animals can be

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characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the GFR α 3 polypeptide.

The important role of GFR α 3 in the survival of peripheral neurons has been confirmed following the discovery of its native ligand, artemin (neublastin). Moreover, knock-out mice in which the GFR α 3 gene was disrupted, generated as taught in the present application, confirmed that GFR α 3 is required for migration and survival of the superior cervical ganglion. See Nishino *et al.*, *Neuron* 23:725-736 (1999), a copy of which was submitted with the Information Disclosure Statement filed on April 27, 2001 and received in the Patent and Trademark Office on May 1, 2001. Such transgenic mice could not have been produced and used without applicants' identification and disclosure of the nucleic acid sequence encoding murine GFR α 3.

The polypeptide of SEQ ID NO: 5 is a mouse GFR α 3 receptor. Although nucleic acids and polypeptides may have different utilities, utility of a polypeptide also establishes utility for the nucleic acid encoding such polypeptide.

The specification, in the passage bridging pages 28 and 29, provides that "[a]gents which bind to the GFR α 3 molecule could be useful in the treatment of diseases or conditions involving the peripheral nervous system," such as "peripheral neuropathies associated with diabetes, HIV, chemotherapeutic agent treatments" and neuropathic pain. In the same section "antagonists" of GFR α 3 are stated to be useful "to treat chronic pain of non-neuropathic nature, such as ... that which is associated with various inflammatory states." The inventors proceed by explaining that these asserted utilities "are consistent with the data of Example 5 in which a strong expression of GFR α 3 within the developing and adult sensory ganglia was observed." At page 29, lines 9-14, the inventors further note that "The surprising, relative lack of expression of GFR α 3 in many organs, including notably brain, gut, and kidney indicates that the ligand (and other agonists and antagonists) which binds this receptor lacks some side effects which may be associated

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with ligands which bind to GFR α 1 and GFR α 2 (GDNF and neurturin). Thus, ligands which act via GFR α 3 will be particularly useful to treat disorders of the peripheral nervous system while including fewer effects on weight loss, motor functions, or on kidney function than would ligands acting via GFR α 1 or GFR α 2.”

According to the definition provided at page 15, lines 8-10, the term “ligand” is used to refer to a molecule which is able to bind to the extracellular (x-subunit receptor of interest, or a known agonist thereof. Accordingly, the term “ligand” is not limited to the native biological ligand of a receptor. Indeed, on pages 29-33, the specification provides a detailed disclosure of anti-GFR α 3 antibodies, which are clearly within the scope of “ligands” as defined for the purpose of the present invention.

Application of the law

The totality of the disclosure provided in the specification reasonably conveyed to one skilled in the art at the effective filing date of this application that agents (including antibodies) which bind to GFR α 3 find utility in the treatment of neuropathies associated with the peripheral nervous system, and chronic pain, whether neuropathic or non-neuropathic in nature.

According to the Examiner, the specification discloses a “laundry list” of utilities, therefore, it merely invites one skilled in the art to discover which specific disease states should be treated. This assertion is believed to be entirely misplaced. As noted above, the disclosure of the present application consistently states the involvement of GFR α 3 in the regulation of peripheral neuronal function, such as in peripheral neuropathies and pain. This specific disclosure, which is supported by the data disclosed in Example 5, can hardly be characterized as involving a “laundry list” of utilities, and qualifies a “specific utility” within the meaning of 35 U.S.C. § 101.

The asserted utility is also “substantial,” since it provides a real world utility in a currently available form.

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The asserted utility is not based in any way on the discovery of putative ligands of GFR α 3 that were not known in the art at the effective filing date of the present application. In view of the teaching of the specification, the knowledge of the native ligand, or the discovery of "putative" agonists or antagonists is not required to utilize the invention for the stated purpose. Antibodies specifically binding GFR α 3 could be readily generated at the filing date of this application, both based on the detailed teaching in the specification, and on general knowledge in the art. The use of such antibodies to treat the indicated conditions was well within the skill of the art at the relevant time frame. Accordingly, the stated specific utility was currently available as of the filing date, and is also "substantial."

It is emphasized that the utility should be examined in the context of the claimed invention. The claims are not directed to the identification of the native ligand, or any "putative" ligand of GFR α 3, and the invention as claimed has utility without such discovery.

Finally, the logic underlying the asserted specific and substantial utility is not seriously flawed, therefore, one skilled in the art would have found the stated utility "credible" at the effective filing date of this application.

It is submitted that the teaching provided in the present application as filed, and in view of subsequent confirmatory data, meets the utility requirement of 35 U.S.C. § 101. Accordingly, applicants respectfully submit that claims 86-97 are directed to subject matter having specific, credible, and substantial utility.

CONCLUSION

Since the claimed invention is supported by a specific and substantial asserted utility, the Examiner is respectfully requested to consider and allow claims 86-97. All claims pending in this application thus being believed to be in *prima facie* condition for allowance, an early issuance of a Notice of Allowance is respectfully solicited.

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Should the Examiner find that there are any issues outstanding, he is respectfully invited to contact the undersigned attorney at the telephone number indicated below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641.

Respectfully submitted,

Dated: January 22, 2003

By: _____

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